allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. Specifically, the Examiner contends that Applicant's specification does not contain a sufficiently explicit disclosure to enable one skilled in the relevant field to practice the invention claimed *without undue experimentation*. Applicant respectfully traverses.

Introduction

The following comments apply generally to the Office Action and serve to frame Applicant's response:

1. The Examiner makes constant reference to the value of data from CETP-transgenic mouse, transgenic rabbit and cholesterol-fed rat models. Applicant needs to clarify that **there are no data presented in this application utilizing a CETP-transgenic mouse or a transgenic rabbit or a cholesterol-fed rat to demonstrate the methods of the invention.** Example I of the invention utilized normal mice to demonstrate the effectiveness of the CMV promotor enhancer for expressing exogenous protein in mammalian muscle, and the remainder of the working examples utilize a New Zealand white rabbit model of atherosclerosis described in Daley et al., *Arterioscl. Thromb., 14*: 95 - 104 (1994). Thus, several of the Examiner's assertions and interpretations of the Applicant's data are simply mistaken.
2. The Examiner makes several references to the unpredictability of "transgenic technology" and gene therapy, as if these fields related to the methods of the present claims. Applicant hastens to clarify that **the present invention does not involve gene therapy.** Rather, the present invention involves the use of a DNA vaccine, calling for transient expression of a peptide vaccine in tissues of a host mammal, in order to produce an *in situ* immune response eliciting production of native antibodies capable of binding endogenous CETP of the host. Applicant's invention does not seek the production of transgenic subjects and does not require gene replacement in a subject. Thus, the Examiner's comments on the complexity and unpredictability of the arts of transgenic technology and gene therapy, while interesting, have been regarded as irrelevant to the present invention.

Applicant respectfully submits that every aspect of the claims has been supported in the specification by ample description and a working example in a mammalian model that is relevant and widely accepted in the field of cardiovascular health. In view of the working examples and the data and descriptions provided in the application, it is submitted that a person skilled in the art would readily believe that the Applicant's results would be obtainable in other mammalian subjects, including humans, by following the teachings of the application. It is submitted, furthermore, that sufficient description, examples and data are provided in the application for a person skilled in the art to practice the methods of the claims and to obtain the results demonstrated, without having to resort to more than routine experimentation. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112 is respectfully solicited, for the reasons set forth in detail below.

The requirement of enablement under 35 U.S.C. §112, first paragraph

"Whether making and using an invention would have required undue experimentation, and thus, whether a disclosure is enabling under 35 U.S.C. § 112 ... is a legal conclusion based upon underlying factual inquiries." *Johns Hopkins University v. CellPro, Inc.*, 152 F3d. 1342, 1354, 47 USPQ2d 1705, 1713 (Fed. Cir. 1998). Factors to be considered in determining whether a disclosure would require "undue" experimentation include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of the routineer in the art, (7) the predictability or lack thereof in the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." *Ex parte* Forman, 230 USPQ 546, 547 (BPAI 1986).

It is incumbent on the Examiner in rejecting claims under the first paragraph of 35 U.S.C. §112 to establish a *prima facie* case of lack of enablement. *In re Strahilevitz*, 668 F.2d 1229, 1232; 212 USPQ 561, 563 (CCPA 1982). In determining whether or not a disclosure is

enabling, it has been consistently held that the enablement requirement of 35 U.S.C. §112, first paragraph, requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); and in meeting the enablement requirement, an applicant's specification need not teach, and preferably omits, that which is well-known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

How the enabling teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance, since the specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. §112 unless there is a reason to doubt the objective truth of the statements relied upon for enabling support. *In re Marzocchi*, 439 F.2d at 223, 169 USPQ at 369 (CCPA 1971). A specification is considered to be enabling if a person skilled in the art could "make and use" the claimed invention without "undue experimentation". *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

In the Office Action, the Examiner attempts to analyze the invention according to the guidance factors set forth by the CAFC in *In re Wands*, to support a conclusion that one skilled in the art could not practice the methods of the subject claims without undue experimentation. Applicant traverses the conclusion of the Examiner as set forth below.

The nature of the invention, breadth of the claims, amount of guidance presented

Applicant notes that the Examiner has mischaracterized the nature of the subject invention. The Examiner states:

> "The claimed invention was based on a hypothesis that the CETP-expressing transgenic murine model is an art-recognized model for atherosclerosis, and that increased levels of CETP activity may be predictive of increased risk of cardiovascular disease…On the basis of applicant's showing of the hypothesis using transgenic mice model, which illustrates that an increased levels of CETP activity may be predictive of increased risk of cardiovascular disease, and of applicant's rabbit model for atherosclerosis, applicant contemplates and claims that any of applicant's claimed plasmid based vaccines can be used to provide a therapeutically or prophylactically cardiovascular benefit in any animal or a human subject or patient." (Office Action, pages 3-4).

Applicant's invention involves DNA plasmid-based vaccines that comprise a plasmid DNA molecule containing a DNA sequence encoding an immunogenic fusion polypeptide having at least one T cell epitope portion and at least one B cell epitope of CETP. When administered to a mammalian subject, the DNA plasmid-based vaccine, upon expression of the immunogenic fusion protein, will induce the production of autoantibodies specifically reactive with endogenous CETP. Said antibodies inhibit endogenous CETP activity or remove (clear) CETP from circulation, in turn promoting an anti-atherogenic serum lipoprotein profile (for example, increased HDL levels and decreased LDL levels), and in turn leading to the inhibition of the development of atherosclerotic lesions. Raising HDL levels, diminishing endogenous CETP activity, and even reduction of atherosclerotic lesions in vaccinated subjects are shown in the application (see, Examples III-IV).

Consistent with the teachings of the specification relating to the benefits of increased HDL levels and the identification of CETP as a therapeutic target, Applicant has developed the above-described DNA-based vaccines as an option for practitioners in treating their patients for hypercholesterolemia. Applicant notes that the DNA vaccines *per se*, the vaccine peptides expressed following administration of such DNA vaccines, as well as the methods of administering the vaccine peptides to mammals, have already been patented by Applicant and his colleague, Charles Ritterhaus. (See, U.S. Patent Nos. 6,284,533; 6,410,022; and 6,555,113.)

Applicant now pursues in the present application claims to the use of such DNA-based vaccines enabling the *in vivo* expression of vaccine peptides as a viable method of administration to a patient in need. Applicant asks the Examiner to note that this is NOT gene therapy, but rather the transient expression of the immunogenic vaccine peptide which triggers the production of autoantibodies to CETP, which in turn is shown to have beneficial effects including: inhibiting endogenous CETP activity or removing CETP from circulation, promoting an anti-atherogenic serum lipoprotein profile (for example, increased HDL levels and decreased LDL levels), and inhibiting the development of atherosclerotic lesions.

The main thrust of the Examiner's lack of enablement rejection appears to be a concern that the claimed methods (including the vaccine peptides) may not be efficacious or even work at all in humans. Although that is a legitimate concern for other agencies, it is misplaced here. As the CAFC has stated:

> "The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human [use]. Simply stated, approval of the Food and Drug Administration is not a prerequisite for finding a [treatment] useful within the meaning of 35 U.S.C. §112, first paragraph. Only objective enablement is required." *In re Brana*, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995).

With respect to the Examiner's argument that the claimed methods may include inoperative embodiments, efficacy problems, or potential side-effects, Applicant points out that it is not the function of the claims to specifically exclude all possible inoperative embodiments. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984).

Applicant's claims cannot supplant and do not seek to supplant the wisdom and training of the practitioner in deciding whether or not to practice the invention. The Applicant is only responsible for describing how to put the methods of the invention into practice. If there are circumstances under which the methods of the invention should not be practiced, for example for medical reasons, that is for the practitioner to decide. But whether or not the practice of the invention is advisable under all circumstances is not a requirement of 35 U.S.C. §112, first paragraph. The relevant inquiry here is whether the practice of the invention is possible for the skilled person, given the information contained in the specification. Applicant has provided sufficient information and exemplification to practice the invention in mammalian subjects and to obtain the desired results. He has therefore satisfied the requirements of 35 U.S.C. §112, first paragraph, and no additional, non-statutory requirements should be held against the claims.

The state of the prior art, the unpredictability of the art, and the relative skill of those in the art

Regarding the "state of the prior art" consideration factor set forth in *In re Wands*, the Examiner contends:

> "[N]o prior art from the time the invention was made until now has demonstrated that any DNA vaccine, has been successful in treating an atherosclerotic patient in the real world as intended by applicants at the time the invention was made." (Office Action, page 4.)

Applicant has demonstrated, in this application, that DNA-based vaccine peptide vaccination for the production of autoantibodies against endogenous CETP is an effective method for inhibiting endogenous CETP activity, promoting an anti-atherogenic serum lipoprotein profile, and inhibiting the development of atherosclerotic lesions. In the present application, Applicant teaches DNA-based vaccines that effectively express *in vivo* the immunogenic fusion peptide encoded by the DNA vaccine and obtain each of the results recited in Applicant's claims. The contention that no "real world" DNA vaccine immunization successfully treating an atherosclerotic patient is of no moment and is also not a requirement of 35 U.S.C. §112. If it were the case that public announcement of successful medical treatment was a standard of enablement, then the function of the Patent Office would be performed by medical journals and press releases.

The data provided in Applicant's specification supports the methods of the claims, and corroborative demonstrations in the general press are not required by 35 U.S.C. §112, first paragraph. Accordingly, it is respectfully submitted that the Examiner's comments do not raise an issue of enablement within the meaning of 35 U.S.C. §112.

The Examiner additionally contends that the methods of the present invention might not work in humans and that the data do not correlate across animal species. For support, the Examiner refers to Gordon et al. (1989), *The New England Journal of Medicine*, 321(19): 1311-1316 (hereinafter *Gordon*), and cites the following passage:

> "The association of lower HDL levels with higher rates of coronary disease within populations in observational epidemiologic studies has given rise to the hypothesis that interventions that raise low levels of HDL cholesterol will reduce coronary disease rates. However, neither our present understanding of lipid metabolism nor these epidemiologic observations can provide assurance that low levels of HDL cholesterol are a causative rather than a coincidental factor in coronary disease, or that intervention would be beneficial." (*Gordon*, page 1314.)

Applicant submits that this point of the Examiner's also goes to the decision of whether to practice the invention and not the enablement to practice the invention. However, considering the reference to *Gordon*, the Examiner ignores the numerous other teachings within *Gordon* that

overwhelming suggest that increasing HDL in relation to LDL is an effective therapeutic prophylactic treatment for atherosclerosis. For example:

> "The recent publication of the results of the Helsinki Heart Study - in which simultaneous 11 percent increases in HDL and reductions in low-density lipoprotein (LDL) cholesterol levels during gemfibrozil therapy were accompanied by a 34 percent reduction in myocardial infarction rates - has raised the issue of whether efforts to increase HDL levels should now be undertaken in patients with elevated or 'normal' total cholesterol levels." (*Gordon*, page 1311.)

See also:

> "In the decade since the first published results of the Honolulu, Framingham, and Tromso studies, **the independent, strong, inverse relation between levels of HDL cholesterol and coronary heart disease has been confirmed with few exceptions by epidemiologic studies in several countries**...A trend relating lower levels of HDL cholesterol to higher rates of coronary heart disease was apparent in most of the studies." (*Gordon*, page 1313.)

From the above it is clear that the *Gordon* reference actually supports the premise of Applicant's invention, i.e., that reducing CETP activity and increasing the level of HDL in proportion to LDL will have a beneficial effect on patients (including humans) suffering from, or at risk of developing, atherosclerosis. Moreover, as previously noted, it is not incumbent on the Applicant to convince the Patent Office that the practice of the invention is medically beneficial. Likewise, it is not a requirement that the specification convince the practitioner that the invention MUST be practiced; the question for patentability is whether the specification explains to the practition how the invention CAN be practiced.

Applicant's methods are objectively enabled by the specification. Applicant has shown that immunogenic fusion proteins expressed according to the methods of the present invention are effective as a means for stimulating an immunological response against a patient's endogenous CETP, which in turn increases HDL levels in relation to LDL. The prior art is consistent with Applicant's teaching that increasing HDL levels can be a method of treating preventing atherosclerosis. And following the Examiner's own citation, *Gordon*, it is evident that a person skilled in this art would accept the teachings of Applicant's specification.

Moreover, in the present application Applicant has shown that plasmid-based vaccines are capable of eliciting the autoimmune response against endogenous CETP by transient expression (**not gene replacement**) of the DNA encoding the fusion polypeptide vaccine.

With regard to the Examiner's contention that rabbit models are not predictive of human or other mammalian activity, Applicant submits the following references:

- Prior et al., " The Hypercholesteremic Rabbit: An Aid to Understanding Arteriosclerosis in Man," *Archives of Pathology*, 71:82-94 (1960);
- Bocan et al., "HMG-CoA reductase and ACAT inhibitors act synergistically to lower plasma cholesterol and limit atherosclerotic lesion development in the cholesterol-fed rabbit," *Atherosclerosis*, 139:21-30 (1998);

Such references demonstrate the wide historical and current acceptance of the rabbit model as a predictive model for atherosclerosis in humans, and they validate the Applicant's contention that the rabbit model data of the present application would be accepted by persons skilled in this art as enabling application of the method to other mammalian subjects in addition to rabbits.

Similarly to *Gordon*, the Examiner cites Assmann et al., *J. Cardiovasc. Pharmacol.*, 16(9):S15-S20 (1991) (hereinafter *Assmann*), to show that further study is still required to fully understand the precise biochemistry involved. *Assmann* states:

> "[T]he complexity of the processes involved in HDL metabolism makes it likely that besides HDL cholesterol reductions that predispose to arteriosclerosis, there will also be those that are not associated with a particular risk...the detailed further analysis of genetic and secondary HDL deficiency syndromes as well as the identification of the precise biochemical mechanisms underlying reversed cholesterol transport remain a challenge in the understanding of the role of HDL in atherosclerosis." (*Assmann*, Abstract.)

Again, Applicant believes that this quote from *Assmann* only relates to WHETHER a practitioner decides to employ Applicant's methods, not to the ENABLEMENT of a practitioner to practice Applicant's methods. If, contrary to the weight of authority represented by the myriad studies cited in *Gordon*, in Applicant's specification, and in the publications of record, a skilled person does not believe that CETP is an appropriate therapeutic target, then that practitioner can choose not to practice the present invention. The present invention presumes that control of CETP activity and increasing serum HDL are appropriate objects, and those presumptions are not a part of the invention. Applicant's invention provides methods for addressing those targets and

achieving modulation of CETP activity and increasing HDL levels using a DNA-based vaccine method. The inquiry under 35 U.S.C. §112, first paragraph, is whether a practitioner is capable of carrying out the Applicant's claimed methods, not whether the therapeutic target is valid or not.

On page 5 of the Office Action, the Examiner continues,

> "The evidentiary support as indicated above not only expresses doubts as to applicant's contemplation and claim of therapeutic application of any DNA plasmid based vaccine expressing any CETP peptide as a magic bullet to treat any atherosclerotic disease in an atherosclerotic patient, let alone subject at risk of having a cardiovascular disease, but also clearly indicates that while transgenic technology may be valuable in studying [the] atherosclerotic process and various risk factors that contribute to the process, the **transgenic model** is not the same as therapeutic application of CETP expressing plasmid based vaccine in treating any animal or human so as to provide a cardiovascular benefit as contemplated by applicant." (Office Action, page 5-6) (emphasis supplied)

Applicant demurs. Since Applicant's specification does not use a transgenic model to explain the presently claimed methods to the person skilled in the art, the Examiner's statement exposes no deficiency in Applicant's disclosure. The models used in the working examples are completely appropriate for describing and demonstrating the effectiveness of the methods as presently claimed, and accordingly no issue under 35 U.S.C. §112, first paragraph, is seen to arise.

The Examiner concludes,

> "Notwithstanding that fact that more than 6 years after the effective filing date of the claimed invention, there is no evidentiary support from any prior art as a result of examiner's exhaust[ive] prior art search, which indicates that CETP peptide expressing plasmid based vaccines can be used therapeutically or prophylactically in treating any real world-animal or human at risk of or having a cardiovascular disease, the following prior art further teaches that an extrapolation from mice or rabbit models to a reasonable enablement of a prophylactic or therapeutic application of CETP peptide expressing plasmid based vaccines in treating a human remains complex and unpredictable." (Office Action, page 6)

Applicant respectfully submits that the rabit model used in the working examples is widely accepted in the art and has been relied on, particularly, to predict the efficacy of drug candidates as treatments for anti-anterosclerosis treatments. For example, **the statin drugs now on the market and available to patients and practitioners were initially tested in the same model as used by Applicant**. See, e.g., the following articles, copies of which accompany this response:

- Ishida et al., "Comparative effects of simvastatin (MK-733) and pravastatin (CS-5143) on hypercholesterolemia induced by cholesterol feeding in rabbits," *Biochimica et Biophysica Acta*, 1042:365-73 (1990);
- Bischoff et al., "Cerivastatin: pharmacology of a novel synthetic and highly active HMG-CoA reductase inhibitor, *Atherosclerosis*, 135:119-130 (1997);
- Bocan et al., "HMG-CoA reductase and ACAT inhibitors act synergistically to lower plasma cholesterol and limit atherosclerotic lesion development in the cholesterol-fed rabbit," *Atherosclerosis*, 139:21-30 (1998)

See, also, in a publication relevant to the effectiveness of vaccine peptides such as encoded by the plasmid-based vaccines used according to this invention:

- Rittershaus et al., "Vaccine-Induced Antibodies Inhibit CETP Activity In Vivo and Reduce Aortic Lesions in a Rabbit Model of Atherosclerosis," *Arterioscler. Thromb. Vasc. Biol.*, 20:2106-12 (2000) (copy enclosed)

The Examiner has picked out statements from several references, *none of which relates to vaccination of an animal to modulate CETP activity or to treat or prevent atherosclerosis*, to support his argument that certain models are of limited value in predicting success in humans. Applicant, on the other hand, has selected a rabbit model that has been in use in cardiovascular medical research for over 40 years AND has been used in evaluating cholesterol control drugs that are now on the market, in particular the statin drugs. Moreover, Applicant has used this model to demonstrate the use of a plasmid-based vaccine to generate an immune response reactive with endogenous CETP in vaccinated subjects, which response was specific for native CETP, controlled CETP activity, raised HDL-cholesterol, and inhibited the formation of atherosclerotic lesions in vaccinated subjects. The Examiner has pointed to no data in any of the citations that calls the validity of Applicant's working examples into question. On the whole,

therefore, Applicant respectfully submits that a person skilled in this art, who by definition is aware of each of the citations of record, would be able to put the Applicant's methods into practice and without undue experimentation determine that the methods had been effective as taught by Applicant.

Although the Examiner's citations, or the portions of them quoted in the Office Action, might have been used prior to Applicant's invention to show that the Applicant's course of investigation proceeded against the general teaching of the art, the data presented in Applicant's specification proves that the reservations of the Examiner's interpretation of the citations are wrong. By following the descriptions and examples of the specification, a person skilled in the art can readily put the methods claimed into use and can readily determine the effectiveness of those methods in raising an antibody response, controlling native CETP activity, altering HDL levels, and achieving an anti-atherosclerotic lipoprotein profile. In view of this, it is submitted that the adequacy of the specification to enable the methods of the claims is clear, and the requirements of 35 U.S.C. §112, first paragraph, have been amply met.

Accordingly, for the reasonse set forth above, reconsideration and withdrawal of the rejection of Claims 17-35 under 35 U.S.C. §112, first paragraph, are respectfully solicited.

Respectfully submitted,

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Date

Michael R. Wesolowski